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QUATERNARY DERIVATIVES OF NOROXYMORPHONE  
WHICH RELIEVE NAUSEA AND EMESIS

BACKGROUND OF THE INVENTION

15

The administration of therapeutic doses of morphine and other clinically useful narcotic analgesics is often accompanied by unpleasant side effects on the gastrointestinal system. For instance, morphine and related opiates such as meperidine and methadone may retard intestinal mobility by causing contractions of the small bowel circular smooth muscle.

20

Morphine and related narcotics may also induce nausea and increased mobility of the gastro-intestinal tract resulting in emesis or vomiting. These side effects are caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. (Goodman and Bilman, The Pharmacological Basis of Therapeutics, p. 502 [6th ed. 1980], incorporated herein by reference.) Studies have shown that morphine and other narcotics cause emesis in dogs. For example, Wang and Glaviano, JPET 111:329-334 (9143), incorporated herein by reference, reported that administration of 0.5 mg/kg of morphine intravenously to 12 dogs resulted in emesis in 9 dogs within an average of 2.4 minutes. (Mg/kg refers to milligrams of morphine per kilograms of body weight.) When 1.0 mg/kg of

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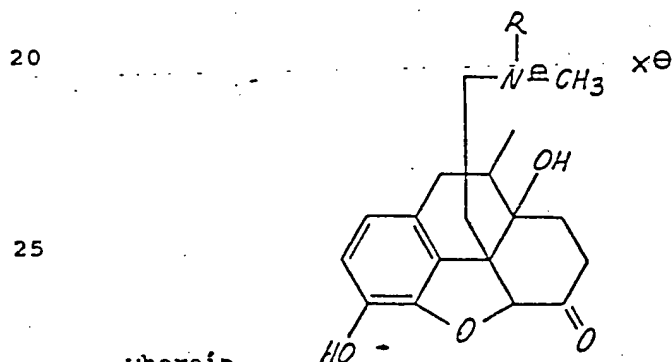
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1 morphine was administered intramuscularly to 13 dogs, 12  
of them vomited within an average time of 3.5 minutes.

SUMMARY OF THE INVENTION

5 U. S. Patent No. 4,176,186 to myself and others  
disclosed treatment of intestinal immobility associated  
with the use of narcotic analgesics through the  
administration of quaternary derivatives of  
10 noroxymorphone. It has now been discovered that the  
same compounds are also useful for the treatment, both  
prophylactic and therapeutic, of the nausea and vomiting  
associated with the administration of these drugs.

15 According to the invention, therefore, nausea and  
vomiting by warm-blooded animals receiving morphine and  
related opiates, meperidine, methadone or the like, may  
be prevented or relieved by the administration of  
methylnaltrexone or other quaternary derivatives of  
noroxymorphone represented by the formula:



wherein

30 R is allyl or a related radical such as  
chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride,  
bromide, iodide or methylsulfate anion.

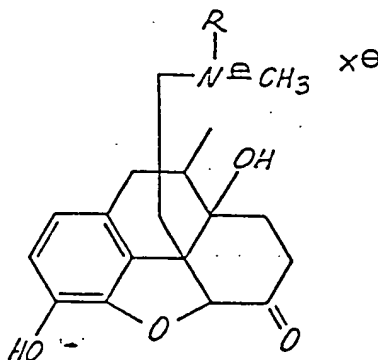
35 These compounds are administered to the animal  
either prior to or simultaneously with the  
administration of the narcotic analgesic. They may be

1 administered either enterally or parenterally. There  
has not been observed any interference with the  
analgesic activity of the opiates.

As used herein, unless the sense of the usage  
5 indicates otherwise, the term "morphine" refers to any  
narcotic analgesic.

#### DETAILED DESCRIPTION

10 This invention relates to the use of quaternary  
derivatives of noroxymorphone to prevent or relieve  
nausea and vomiting associated with the administration  
of morphine to warm-blooded animals. The useful  
compounds are represented by the formula:



wherein

R is allyl or a related radical such as  
25 chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride,  
bromide, iodide or methylsulfate anion.

The compounds are synthesized as described in  
United States Patent No. 4,176,186, the disclosure of  
30 which is incorporated herein by reference. A  
particularly preferred noroxymorphone derivative is  
methylnaltrexone, but other compounds represented by the  
above formula are also suitable.

35 Methylnaltrexone or other noroxymorphone  
derivatives may be administered to the patient either

enterally or parenterally. However, a preferred method of administration is by injection. Nausea and emesis may follow after even a single dose of morphine, unlike intestinal immobility which is usually the effect of chronic repeated usage of the drug. Consequently, it is contemplated that the patient will be given an injection of methylnaltrexone prior to surgery or other occasion when morphine is used to treat acute pain.

As illustrated by the following Controls and Examples, our studies show that methylnaltrexone inhibits emesis when administered either together with the morphine or before the morphine is administered. It is thought that methylnaltrexone or other quaternary noroxymorphone derivatives may be administered up to two hours before the administration of morphine, but that period may be variable. In our studies, methylnaltrexone was administered intramuscularly by means of a syringe. Methylnaltrexone may also be administered enterally or parenterally by other means. It has been found to be effective in dosages in the range of about 0.05 mg/kg to about 1.0 mg/kg for each 1 mg/kg of administered morphine. It was found effective when administered in the same syringe as morphine and also when administered up to about one hour before the administration of morphine.

The effect of methylnaltrexone in reversing the emetic effects of morphine is illustrated herein. The unit of mg/kg refers to milligrams of substance administered per kilograms of body weight.

#### CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered intramuscularly to five dogs. Four dogs vomited. In each instance, vomiting occurred within four minutes. On a different day the same dose of morphine was

1 administered intramuscularly to the same five dogs in  
the same syringe with 1 mg/kg of methylnaltrexone. None  
of the dogs vomited.

5 CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg  
of morphine. All six dogs vomited. On an additional  
day the same dose of morphine was combined with 0.5  
mg/kg of methylnaltrexone and administered in the same  
10 syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered  
intramuscularly to three dogs. All three dogs vomited.  
15 On an additional day the morphine was combined with 0.25  
mg/kg of methylnaltrexone and administered in the same  
syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

20 Methylnaltrexone was administered to two dogs prior  
to the administration of 1 mg/kg morphine. In one dog,  
0.5 mg/kg of methylnaltrexone was administered  
intramuscularly 15 minutes before the morphine. No  
vomiting occurred. In the second dog, the same dose of  
25 methylnaltrexone was administered 30 minutes before the  
administration of morphine. No vomiting occurred.

CONTROL 5 AND EXAMPLE 5

0.05 mg/kg methylnaltrexone was administered  
30 intravenously to four dogs one minute prior to the  
administration of 1.0 mg/kg morphine. No vomiting  
occurred in any of the dogs. On a different day, the  
same animals were given 1.0 mg/kg morphine without the  
administration of methylnaltrexone. All four dogs  
35 vomited.

1       The administration of methylnaltrexone alone was  
found to produce no noticeable effects in the animals.  
Previous studies with larger doses of methylnaltrexone  
5       have demonstrated that unlike the non-quaternary  
naltrexone, methylnaltrexone does not precipitate  
withdrawal systems in morphine-tolerant dogs. Russell  
et al., Eur. J. Pharmacol. 78:255-261 (1982),  
incorporated herein by reference. Methylnaltrexone has  
10       not been found to interfere with the analgesic activity  
of morphine or narcotics.

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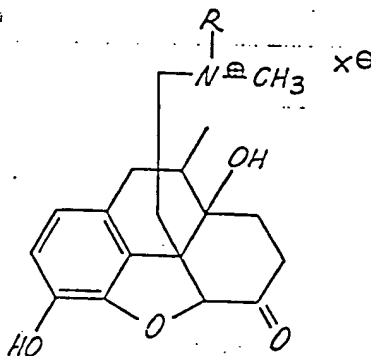
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WHAT IS CLAIMED IS:

1. A method for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm-blooded animals, which comprises administering to an animal prone towards nausea or emesis on receiving narcotic analgesics, an effective amount of at least one nausea and emesis relieving compound of the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion, prior to or simultaneously with administration of the narcotic analgesic.

2. A method as claimed in claim 1, where the compound is administered to the animal in an amount between about 0.05 mg/kg and about 1.0 mg/kg.

3. A method as claimed in claim 1, where the compound is administered to the animal enterally.

4. A method as claimed in claim 1, where the compound is administered to the animal parenterally.



1           5. A method as claimed in claim 4, where the  
compound is administered to the animal by injection.

5           6. A method as claimed in claim 1, where the  
compound is administered to the animal prior to the  
administration of the narcotic analgesic.

10          7. A method as claimed in claim 6, where the  
compound is administered to the animal up to about two  
hours prior to the administration of the narcotic  
analgesic.

15          8. A method as claimed in claim 1, where the  
compound is administered to the animal concurrently with  
the administration of the narcotic analgesic.

          9. A method as claimed in claim 1, where the  
compound comprises methylnaltrexone.

20          10. A method for preventing or relieving nausea  
and emesis associated with the use of narcotic  
analgesics in warm-blooded animals, which comprises  
administering to an animal prone to exhibit nausea or  
emesis on administration of narcotic analgesics,  
25          methylnaltrexone in the amount of between about 0.05  
mg/kg and about 1.0 mg/kg simultaneous with or up to  
about two hours prior to the time of administration of  
the narcotic analgesic.

30          11. A method as claimed in claim 10, where the  
methylnaltrexone is administered to the animal  
parenterally.

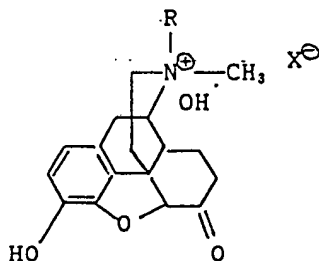
QUATERNARY DERIVATIVES OF NOROXYMORPHONE  
WHICH RELIEVE NAUSEA AND EMESIS

ABSTRACT OF THE DISCLOSURE

Quaternary derivatives of noroxymorphone are used to prevent or relieve nausea and emesis associated with the use of narcotic analgesics without interfering with the analgesic activity of the drugs. A particularly preferred compound is methylnaltrexone. The compound is administered in a concentration between 0.05 mg/kg and 1.0 mg/kg prior to or concurrently with the administration of the narcotic analgesic.

Claims:

1. A medicament for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm blooded animals comprising as an active principle at least one nausea and emesis relieving compound represented by the general formula:



wherein

R is an allyl, chloroallyl, cyclopropyl-methyl or propargyl radical, and

X is the anion of an acid.

2. The medicament according to Claim 1 wherein X is selected from the group consisting of a chloride, bromide, iodide or methyl-sulfate anion.

3. The medicament according to Claim 1 wherein the compound comprises methylnaltrexone.